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Stereoselective Transaminase-Mediated Synthesis of Serotonin and Melatonin Receptor Agonists

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Abstract: Transaminase enzymes have significant potential for the stereoselective synthesis of drugs or drug precursors. Here, starting from one prochiral β-tetralone, a short and efficient chemoenzymatic synthesis of four agonists of the serotonin/melatonin receptors have been developed. The key step is the stereoselective transamination of the prochiral ketone to produce both enantiomers of 8-methoxy-2-aminotetraline in high yields and enantiomeric excesses. This was followed by either amidation to give the 8-methoxy-2-acetimidotetralines or several facile chemical steps to the 8-hydroxy-2-aminodipropyltetralines.

Keywords: biocatalysis; transaminases; aminotetralines; chemoenzymatic

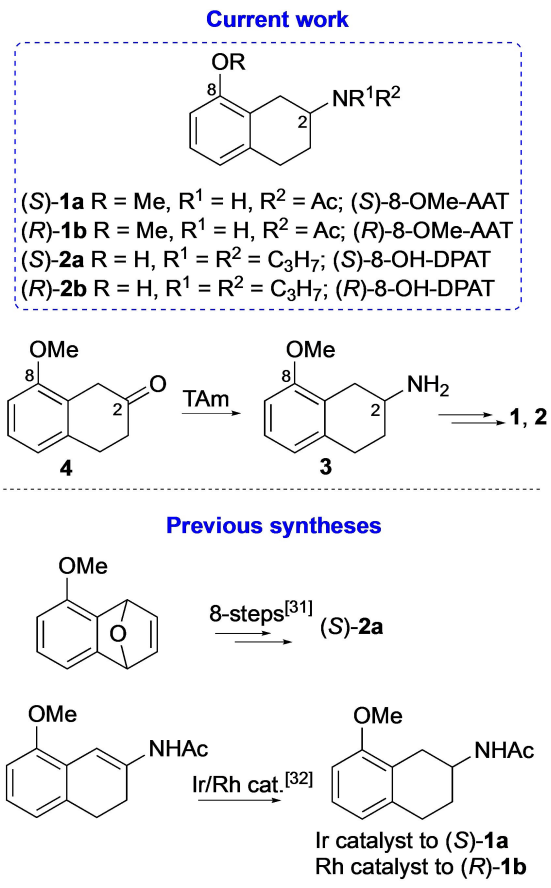
Introduction

In recent years, biocatalytic methods have become increasingly important for the sustainable synthesis of fine chemicals and pharmaceuticals. One of the most promising enzymes used in recent years are transaminases (TAms, EC 2.6.1) which catalyze the transfer of an amino group from an amine donor to a ketone or aldehyde and require the co-factor pyridoxal 5'-phosphate (PLP).[1–3] Using TAms, amines have been produced in high yields, regio- and stereoselectivities using mild reaction conditions, highlighting them as valuable catalysts for use in synthesis. Examples include the synthesis of single isomer pharmaceutical ingredients, other chiral synthons or biologically active compounds, as well as small molecule amines not readily accessible via traditional synthetic routes.[4–10] Notably TAms have been reported to accept a wide range of substrates from acyclic ketones and hydroxyketones to cyclic and aromatic ketones.[3–7,9–12]

Aminotetralines are important chiral motifs found as single-isomers in a number of pharmaceuticals including the 1-aminotetraline antidepressant Norsertraline, and 2-aminotetralines such as the dopamine β-hydrolase inhibitor Nepicastat and dopamine receptor agonist Rotigotine used for the treatment of Parkinson's disease.[13–15] The asymmetric synthesis of 1-aminotetralines using transaminases has been described, as well as their kinetic resolution, including the development of enzyme variants to improve substrate acceptance.[3,12,16–18] Fewer publications have described the TAm-mediated synthesis of 2-aminotetralines, from β-tetralone or 7-methoxy β-tetralone.[12,17,19,20] In one report high yields were noted when using lactate or alanine dehydrogenase enzymes to drive the reactions to generate the amine product,[12] but 8-methoxy-β-tetralones have not been utilised. 8-Hydroxy or methoxy-2-aminotetraline derivatives are important due to their therapeutic applications, for example 8-methoxy-2-acetimidotetraline **1** (8-OMe-ATT) has been used as a melatonin agonist with

affinity predominantly arising from the (*S*)-**1a** isomer (Scheme 1).[21–23] Also, aminotetralin **2**, 8-OH-DPAT has been extensively reported in the literature as a potent 5-HT1A serotonin agonist, frequently used for studying serotonergic mechanisms. Studies established that the (*S*)-isomer **2a** was a partial agonist, while the (*R*)-isomer **2b** was a full agonist, and in experiments **2** has been described as having many effects from antidepressant to bradycardic, as an analgesic and a 5-HT7 receptor agonist.[24–29]

Due to the importance of this structural motif, there are a number of reports describing achiral syntheses, although there are fewer routes to single isomers of **1** and **2**. Examples include a 6-step synthesis of the precursor (*R*)-**3** from 1-methoxynaphthalene incorporating a naphthalene dioxygenase biocatalytic step,[30] and an asymmetric Rh-catalyzed ring opening reaction as part of an 8-step approach to (*S*)-**2a** (Scheme 1).[31] Recently, asymmetric Ir- or Rh-catalyzed hydrogenations of the cyclic β-enamide have also been reported to generate **1a** and **1b**, respectively.[32] While these provide useful routes to an important class of amines they either require multi-step procedures or use non-sustainable catalysts that in addition require the preparation of the chiral ligand. Very recently, metagenomic imine reductases were described in a chemoenzymatic route to the aminotetraline Rotigotine, which possesses a thiophene group, in 92% enantiomeric excess (ee), highlighting an interesting biocatalytic approach.[33] Here we describe for the first time in a divergent strategy from 8-methoxy-2-tetralone **4**, the use of TAms to generate (*S*)- and (*R*)-8-methoxy-2-aminotetraline **3**, with subsequent conversion into both isomers of the melatonin and serotonin agonists **1** and **2** (Scheme 1).



Scheme 1. The transaminase mediated asymmetric synthesis of 2-aminotetralines **3** in this work and previous approaches.

Results and Discussion

To access the key amine **3**, transaminases able to readily accept **4** were required. For enzyme screening, 25 TAms from the UCL enzyme toolbox were selected based upon activities previously observed in other screening programmes, including 23 (*S*)-selective and two (*R*)-selective TAms (Table 1).[34–40] Enzymes were screened against **4** (5 mM) using (*S*)- or (*R*)-methylbenzylamine (MBA) as the amine donor depending on the selectivity of the enzyme.

The best (*S*)-selective TAm was C*v*TAm[36] with a 96% conversion and the highest yielding (*R*)-selective enzyme was ArRMut11 with a 76% conversion. A further 8 TAms gave >10% yields, highlighting their potential use in amination reactions with analogues. It was also interesting to note that even though **4** is a comparatively large substrate, it was readily accepted by several native TAms. Reactions with *Cv*TAm were then developed to generate (*S*)-**3** for the synthesis of **1a** and **2a**. Isopropylamine (IPA) is often used as a low-cost amine donor, so the amination was studied using IPA and increased concentrations of substrate **4** and enzyme with no effect on the conversions (>95%) (Table 2). Scale-up of the biocatalytic reaction to 100 mL, followed by product isolation using an acid/basic extraction afforded (*S*)-8-methoxy-2-aminotetraline **3a** in 90% yield. In order to determine the enantiomeric excess (ee), a derivatization method with (*R*)- and (*S*)- Mosher's acids was performed as the enantiomers could not be separated by available chiral HPLC columns, and found to be >95%. Having synthesised **3a** in one step from tetralone **4**, in high yield and stereoselectivity, then enables access to **1a** and **2a**.

For the production of tetraline (*R*)-**3b**, ArRMut11 was used which has been described for a number of applications and readily accepts IPA as the amine donor. However, it is typically used at high pH (pH 11)[5] which was not suitable here due to substrate degradation at >pH 8. Also, an experiment was performed using IPA as the amine donor with **4** at pH 7.5 and an HPLC yield of 13% was observed. Therefore, the reaction was explored further with (*R*)-MBA. The main parameters influencing the biocata-

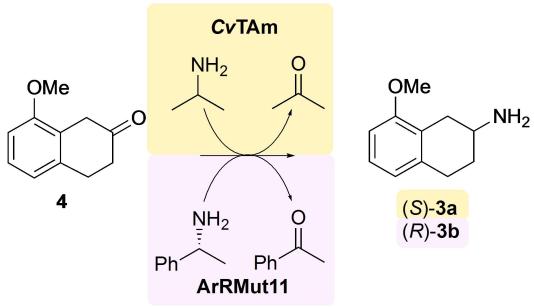
Table 1. Screening results using **4** and 25 selected TAms.[a]

pQR code	Transaminase	(*S*)/(*R*)	Conv.[b]
pQR426	*Pseudomonas aeruginosa* PAO2 PAO_132[34]	*S*	44%
pQR427	*Pseudomonas putida* KT2440 PP_0596[35]	*S*	9%
pQR801	*Chromobacterium violaceum* (*Cv*TAm)[36]	*S*	**96%**
pQR803	*Saccharopolyspora erythrea* DSM40517 SACE_3329	*S*	4%
pQR804	*Saccharopolyspora erythrea* DSM40517 SACE_4673	*S*	3%
pQR806	*Streptomyces avermitilis* DSM46492 SAV_4551	*S*	1%
pQR807	*Streptomyces avermitilis* DSM46492 SAV_2612[35]	*S*	31%
pQR902	*Pseudomonas aeruginosa* PAO2_4382849	*S*	3%
pQR904	*Klebsiella pneumonia* KP_3309659	*S*	3%
pQR906	*Bacillus subtillis* 162 BSU_09260-1971 16079319	*S*	1%
pQR907	*Escherichia coli* MG1655	*S*	3%
pQR914	*Thermus aquaticus* 218243904	*S*	0%
pQR922	*Sulfolobus solfataricus* 13815901[37]	*S*	1%
PQR958	*Pseudomonas putida* PP_3718[35,38]	*S*	17%
pQR959	*Pseudomonas putida* PP_2180	*S*	50%
pQR960	*Bacillus subtillis* BSU_09260-1971	*S*	12%
pQR961	*Bacillus subtillis* BSU_09260-402	*S*	3%
pQR980	*Deinococcus geothermalis* Dgeo_1416[35]	*S*	0%
pQR1003	*Vibrio fluvialis* (*Vf*TAm)[39]	*S*	35%
pQR1005	*Klebsiella pneumonia* KPN_00255[35]	*S*	7%
pQR1006	*Klebsiella pneumonia* KPN_00799	*S*	47%
pQR1017	*Rhodospirillum rubum* RRU_A1254	*S*	2%
pQR1019	*Rhodobacter sphaeroides* RSPH17025_2835[37]	*S*	1%
pQR1048	*Mycobacterieum vanbaaneeli* (*Mv*TAm)[40]	*R*	15%
pQR1049	ArRMut11[5]	*R*	**76%**

[a] *Reaction conditions*: 5 mM **4**, 25 mM (*S*)- or (*R*)-MBA, TAm clarified cell lysates (protein 0.2–0.5 mg/mL), potassium phosphate (KPi) buffer (100 mM, pH 7.5), 1 mM PLP, 30 °C, 500 rpm, 18 h, 10% of methanol (v/v) to a total volume of 200 µL.

[b] Conversions were determined by HPLC analysis based on acetophenone formation (detected at 254 nm). Results were obtained from three independent experiments and varied by $< \pm 5\%$. Reactions were also verified against two negative controls, one without **4** and one with *E. coli* cells containing an empty vector.

Table 2. Transaminase reactions using the enzymes and amine donors indicated and **4** to give **3a** or **3b**.[a]



Conc. **4**	Enzyme/amine donor	Conc. amine donor	Protein conc. mg/mL[b]	Yield **3**[c]
5 mM	C*v*TAm/IPA	25 mM	0.4	**3a** 97%
10 mM	C*v*TAm/IPA	50 mM	0.7	**3a** 97%
15 mM	C*v*TAm/IPA	75 mM	1.0	**3a** 99%
20 mM	C*v*TAm/IPA	100 mM	1.3	**3a** 98%
20 mM[d]	C*v*TAm/IPA	100 mM	1.3	**3a** 90%[e]
5 mM	ArRMut11/(*R*)-MBA	10 mM	0.4	**3b** 99%
10 mM	ArRMut11/(*R*)-MBA	20 mM	0.8	**3b** 96%
15 mM	ArRMut11/(*R*)-MBA	30 mM	1.2	**3b** 98%
20 mM	ArRMut11/(*R*)-MBA	40 mM	1.6	**3b** 98%
20 mM[d]	ArRMut11/(*R*)-MBA	40 mM	1.6	**3b**[e] 81%

[a] *Reaction conditions*: (i) *Cv*TAm- clarified cell lysates, **4**, KPi buffer (100 mM, pH 7.5), PLP (1 mM), 30 °C, 500 rpm, 18 h, 10% methanol (v/v) to a total volume of 200 µL unless otherwise indicated. (ii) ArRMut11-clarified cell lysates, **4**, KPi buffer (100 mM, pH 7.0), PLP (1 mM), 30 °C and 40 °C for the 100 mL reaction, 500 rpm, 18 h, 10% methanol (v/v) to a total volume of 200 µL unless otherwise indicated.

[b] Total protein concentrations in mg/mL.

[c] The yield of **3** was determined by HPLC at 214 nm against product standards unless otherwise indicated.

[d] 100 mL scale reaction.

[e] Isolated yield.

lytic transamination with **4** (buffer and pH, and amine donor, co-factor and substrate concentrations) were studied (Figure 1 and Table 2). The best yields (by HPLC analysis) were obtained with TRIS and KPi buffers, so KPi was selected to make the purification step more straightforward, and 100 mM buffer was preferred. For the amine donor, 2 equivalents of (*R*)-MBA gave good yields (Figure 1 and Table 2).

As mentioned, **4** is unstable above pH 8, indeed at pH 8 a 59% conversion was observed and no product was formed at pH 10; a pH of 7.0 was therefore utilised and 1 mM PLP. Adopting these reaction conditions gave a 99% HPLC yield of **3b** (5 mM of **4**, Table 2). Reactions were then explored at different substrate concentrations on the small scale. High

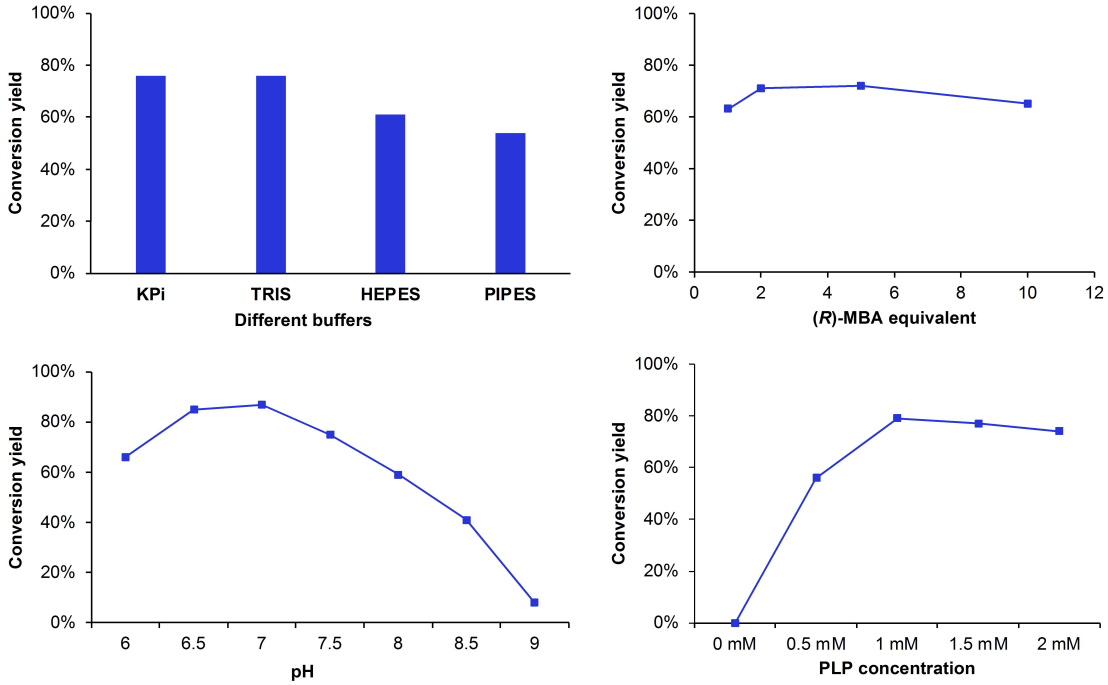
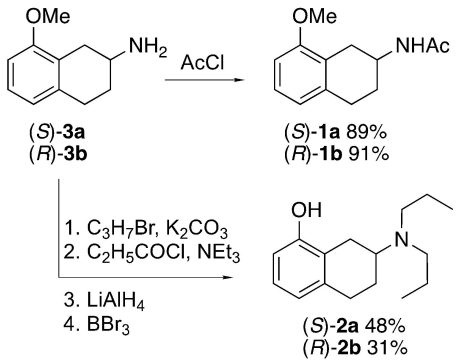


Figure 1. Effect of various parameters for the transamination of **4** with ArRMut11. Yields were based on the formation of **3 b** as determined by analytical HPLC at 214 nm, against product standards. Experiments were performed in triplicate and varied by $< \pm$ 5%.

HPLC yields were achieved (96-98%), so a 100 mL reaction was performed at 40 °C. After 18 h the product was isolated by an acid/basic extraction followed by column chromatography to afford **3 b** in 81% yield and $>$95% ee (via Mosher ester formation and ^{1}H NMR analysis).

Compounds **1 a** and **1 b**, were then readily prepared in 89% and 91% yield respectively using acetyl chloride (Scheme 2). Overall they were synthesised efficiently in 2 steps starting from **4**, giving (*S*)-**1 a** in 80% yield and (*R*)-**1 b** in 74% yield. For the synthesis of (*S*)-8-OH-DPAT **2 a**, **3 a** from the *Cv*TAm transamination reaction was first monoalkylated using bromopropane in 63% yield and then converted with propionyl chloride to the corresponding amide in 89% yield, followed by reduction with lithium aluminium hydride in a 97% yield. Finally, removal of the methoxy group using boron tribromide was achieved in 96% yield. Overall, (*S*)-**2 a** was synthesised starting from tetralone **1** in 5 steps and 48% yield, with only one step requiring purification by column chromatography (Scheme 2). An analogous approach was used for the synthesis of (*R*)-**2 b**, from (*R*)-**3 b** produced by ArRMut11 in the transamination step. Isomer **2 b** was synthesised in 31% yield over 5 steps.



Scheme 2. Synthesis of (*S*)- and (*R*)-8-OH-8-AAT (**1 a** and **1 b**) and (*S*)- and (*R*)-8-OH-DPAT (**2 a** and **2 b**).

Conclusion

In summary, efficient and short chemoenzymatic syntheses of (*S*)- and (*R*)-8-OH-8-AAT (**1 a** and **1 b**) and (*S*)- and (*R*)-8-OH-DPAT (**2 a** and **2 b**) have been described. The key step was the biocatalytic transamination of the prochiral tetralone **4**, in order to obtain both enantiomers of the aminotetraline **3** in high yields and high ees ($>$95%).

Experimental Section

General Experimental

All reagents were obtained from commercial sources (Sigma Aldrich, Fisher, Alfa Aesar) and used as received unless otherwise stated. Silica column chromatography was performed using Geduran® Si 60 Silica (43–60 μM). Thin layer chromatography was performed using plates with a silica gel matrix on an aluminium support. ^{1}H and ^{13}C NMR spectra were obtained using Avance 300 and 500 (Bruker) spectrometers. Chemical shifts specified are relative to trimethylsilane (at 0 ppm) and referenced to the residual, protonated NMR solvent. Coupling constants in ^{1}H NMR spectra (*J*) are given in Hertz (Hz) and described as singlet (s), doublet (d), triplet (t), multiplet (m). Mass spectroscopy was carried out using VG70-SE mass spectrometer Trace 1310 Gas Chromatograph (Thermoscientific) connected to a ISQ single quadrapole MS (Thermoscientific). Melting points were determined using IA9000 Series melting point apparatus (Electrothermal). Analytical HPLC analysis was carried out using a Series 1100 (Hewlett Packard) or 1260 (Aligent Technologies) instrument.

The following centrifuges were used: Allegras x-15R centrifuge (Beckman Coulter), Centrifuge 5415R (Eppendorf), Centrifuge 5810R (Eppendorf), Centrifuge 5430R (Eppendorf). Chemicals, media and apparatus were autoclaved (Priorclave) at 121 °C for 30 min where required.

Preparation of Enzymes

Strains and Plasmids

Strains and plasmids used in this work are listed in the SI Table S1. *E. coli* BL21 (DE3) was used for bioconversions. The plasmid pET-29a(+) was used as the expression vector. Recombinant strains were obtained by introduction of plasmid DNA into the host strains via a heat-shock procedure. Transformants were selected via their antibiotic resistance. Cultivations were carried out at 37 °C or 30 °C in 2xYT medium (16 g/L tryptone, 10 g/L yeast extract and 5 g/L NaCl). For cultivation, an Innova® 44/44R orbital shaker (Eppendorf, Hamburg, Germany) was used at 200 rpm. Kanamycin (Km) was added in concentrations of 50 μg/mL. Solid 2xYT media was prepared accordingly containing 1.5% agar.

Growth, Expression and Cell Lysates Preparation (100 mL or 600 mL)

For pre-cultivation, 5 mL 2xYT medium was inoculated with a single colony and cultivated overnight. Subsequently, 100 mL or 600 mL 2xYT culture was inoculated with 1.6 or 10 mL of the overnight culture, respectively. The cells were grown until the suspension reached an optical density at 600 nm (OD600) of 0.9 and was induced with 1 mM isopropyl-β-thiogalactopyranoside (IPTG) for 6 h at 30 °C before cells were harvested via centrifugation (4650 g, 15 min, 4 °C). The supernatant was discarded and the cell pellet frozen in liquid nitrogen for 15 min and freeze dried overnight. Freeze dried cells were used either directly for cell lysis or stored at −20 °C until usage. Freeze dried *E. coli* BL21 (DE3) TAms were resuspended in KPi buffer (100 mM, pH 7.5) to a concentration of 20–60 g/L cell dry weight (gCDW). Cell lysis was performed by sonication using a Soniprep 150 plus sonicator with microprobe tip (MSE Ltd., London, UK) at a power of 16 Watts for 10 cycles of 15 s on/15 s off. The sonicated suspension was centrifuged (13,000 g, 4 °C, 20 min) and the pellet discarded. The clarified cell lysate was diluted to the desired final protein concentration (e.g. for screening between 0.2 and 0.4 mg/mL protein) and used either immediately in bioconversions or was frozen at −20 °C for a maximum of 1 month.

Initial (S)- and (R)-MBA Screening

(*S*)-MBA (25 mM) or (*R*)-MBA, depending on the enzyme selectivity, PLP (1 mM) in KPi buffer (pH 7.5, 100 mM) and **4** (5 mM in MeOH, 10% v/v final conc.), were added to a 96 well-plate to give a total volume of 180 μL. The reaction was started by the addition of 20 μL of clarified cell extract (final protein conc. of 0.2–0.4 mg/mL). After incubation for 18 h at 30 °C and 500 rpm, the reaction was quenched with 1 μL of TFA and denatured protein was removed by centrifugation. The supernatant (180 μL) was diluted with water (540 μL) and analysed by HPLC using an ACE 5C18-300 column (150 × 4.6 mm) with UV detection at 250 nm. The concentration of acetophenone produced was determined using a linear gradient 15%–72% over 10 minutes at 1 mL/min (A = water with 0.1% of TFA and B = acetonitrile) with subtraction of a negative control without amine acceptor. The acetophenone produced eluted at a retention time of 8.8 min. Results were verified in triplicate against a negative control without amine acceptor following the same procedure.

CvTAm Small Scale Reactions with IPA and 20 mM Substrate

IPA (100 mM, re-adjusted to pH 7.5), PLP (1 mM) in KPi buffer (pH 7.5, 100 mM), and **4** (20 mM from 200 mM stock solution in MeOH, to a 10% v/v final conc.) were added to a 96 well-plate to give a total volume of 135 μL. The reaction was started by the addition of 65 μL of clarified cell extract (final protein conc. of 1.3 mg/mL). After incubation for 18 h at 30 °C and 500 rpm, the reaction was quenched with 1 μL of TFA and denatured protein was removed by centrifugation. The supernatant (180 μL) was diluted with water (540 μL) and analysed by HPLC using an ACE 5C18-300 column (150 × 4.6 mm) with UV detection at 214 nm. The concentration of **3** produced was determined using a linear gradient of 15%-72% over 10 min at 1 mL/min (A = water with 0.1% of TFA and B = acetonitrile) with subtraction of a negative control without amine acceptor. Aminotetraline **3** eluted at a retention time of 6.4 min. Results were verified in triplicate against a negative control without amine acceptor following the same procedure.

ArRMut11 Small Scale Reactions with (R)-MBA and 20 mM Substrate

(*R*)-MBA (40 mM), PLP (1 mM) in KPi buffer (pH 7.0, 100 mM), and the substrate (20 mM from 200 mM stock solution in MeOH, to a 10% v/v final conc.) were added to a 96 well-plate to give a total volume of 120 μL. The reaction was started by the addition of 80 μL of clarified cell extract (final

protein conc. of 1.6 mg/mL). After incubation for 18 h at 30 °C and 500 rpm, the reaction was quenched with 1 µL of TFA and denatured protein was removed by centrifugation. The supernatant (180 µL) was diluted with water (540 µL) and analyzed by HPLC using an ACE 5C18-300 column (150×4.6 mm) with UV detection at 214 nm. The concentration of **3** produced was determined using a linear gradient 15%–72% over 10 min at 1 mL/mL (A = water with 0.1% of TFA and B = acetonitrile) with subtraction of a negative control without amine acceptor. Aminotetraline **3** eluted at a retention time of 6.4 min. Results were verified in triplicate against a negative control without amine acceptor following the same procedure.

Synthetic Procedures

(2S)-8-Methoxy-1,2,3,4-Tetrahydronaphthalen-2-Amine, (S)-3 a

The enzymatic reaction was performed using a total volume of 100 mL, containing IPA (100 mM, 10.0 mmol, with the pH readjusted to 7.5), **4** (352 mg, 20 mM, 2.0 mmol), PLP (1 mM), KPi buffer pH 7.5 (100 mM), *Cv*TAm lysate (final protein conc. 1.3 mg/mL) and MeOH as co-solvent (10% v/v) at 30 °C and 500 rpm for 18 h. The reaction mixture was then acidified and centrifuged, and the supernatant concentrated under vacuum and 50 mL of HCl (0.1 M) added. The aqueous solution was washed with Et_2O (3×100 mL), basified with NaOH (0.2 M) to pH 12 and the product extracted with Et_2O (3×100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford compound **3 a** (316 mg, 1.79 mmol, 90%). $[\alpha]^{20}_D$ −71.4 (*c* 0.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$; 300 MHz) δ 7.08 (1H, t, *J* = 8.4 Hz, 6-H), 6.71 (1H, d, *J* = 8.4 Hz, 5-H or 7-H), 6.67 (1H, d, *J* = 8.4 Hz, 5-H or 7-H), 3.81(3H, s, OMe), 3.18-3.00 (2H, m, 2-H, 1-*H*H), 2.89-2.83 (2H, m, 4-H_2), 2.31-2.23 (1H, dd, *J* = 16.4 and 9.0 Hz, 1-H*H*), 2.00-1.92 (1H, m, 3-*H*H), 1.62-1.51 (3H, m, NH_2, 3-H*H*); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 157.7, 137.5, 126.2, 124.4, 121.0, 107.2, 55.4, 47.3, 33.5, 32.5, 28.6; *m/z* [CI] 178 ($[MH]^+$, 100%); *m/z* [HRMS CI] found 178.1225 $[MH]^+$. $C_{11}H_{16}NO$ requires 178.1226.

(2R)-8-Methoxy-1,2,3,4-Tetrahydronaphthalen-2-Amine, (R)-3 b

The enzymatic reaction was performed using a total volume of 100 mL, containing (*R*)-MBA (485 mg, 40 mM, 4.0 mmol), **4** (352 mg, 20 mM, 2.0 mmol), PLP (1 mM), KPi buffer pH 7.0 (100 mM), ArRMut11 lysate (final protein conc. 1.6 mg/mL) and MeOH as co-solvent (10% v/v) at 40 °C and 500 rpm for 18 h. The reaction mixture was then acidified, centrifuged and the supernatant extracted with Et_2O (3×100 mL). The aqueous phase was adjusted to pH 12 with NaOH (0.2 M) and extracted with Et_2O (3×100 mL). The combined organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The product was further purified by silica column chromatography (92% CH_2Cl_2/8% MeOH) to afford **3 b**[31] (286 mg, 1.62 mmol, 81%). The NMR spectroscopic characterisation data was the same as for **3 a**. $[\alpha]^{20}_D$ +69.7 (*c* 0.5, CH_2Cl_2) [lit. $[\alpha]_D$ +79.8 (c 5.8 mg/mL, $CHCl_3$)[31]]; *m/z* [EI] 177 ($[M]^+$, 100%), 160, 134, 104; *m/z* [HRMS EI] found 177.1148 $[M]^+$. $C_{11}H_{15}NO$ requires 177.1149.

(2S)-N-(8-Methoxy-1,2,3,4-Tetrahydronaphthalen-2-yl)acetamide, (S)-1 a

To a solution of (2*S*)-**3 a** (100 mg, 0.560 mmol) in dry CH_2Cl_2 (20 mL) at rt under argon, was added NEt_3 (235 µL, 1.68 mmol) followed at 0 °C by acetyl chloride (59 µL, 0.84 mmol). The reaction was warmed to rt and stirred for 2 h. It was quenched with the addition of HCl (0.1 M, 10 mL) and the product extracted with CH_2Cl_2 (3×20 mL) and the combined organic extracts were washed with NaOH (0.1 M, 20 mL). The organic layer was then dried ($MgSO_4$) and concentrated under vacuum to afford compound (*S*)-**1 a** (109 mg, 89%). M.p. 107 °C (Et_2O); $[\alpha]^{20}_D$ −25.4 (*c* 0.5, CH_2Cl_2) [lit. $[\alpha]^{20}_D$ −27.0 (*c* 0.1, $CHCl_3$)[41]]; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 7.11 (1H, t, *J* = 8.4 Hz, 6-H), 6.72 (1H, d, *J* = 8.4 Hz, 5-H or 7-H), 6.67 (1H, d, *J* = 8.4 Hz, 5-H or 7-H), 5.54 (1H, br s, NH), 4.33-4.21 (1H, m, 2-H), 3.81 (3H, s, OMe), 3.06 (1H, dd, *J* = 17.3 and 5.6 Hz, 1-*H*H), 2.89-2.83 (2H, m, 4-H_2), 2.44 (1H, dd, *J* = 17.3 and 8.2 Hz, 1-H*H*), 2.06-1.99 (1H, m, 3-*H*H), 1.97 (3H, s, CH_3CO), 1.80-1.68 (1H, m, 3-H*H*); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 169.7, 157.7, 137.1, 126.7, 123.1, 121.2, 107.2, 55.5, 45.1, 29.8, 28.3, 27.3, 23.9; *m/z* [ES+] 220 ($[MH]^+$, 100%); *m/z* [HRMS ES+] found 220.1337 $[MH]^+$. $C_{13}H_{18}NO_2$ requires 220.1338.

(2R)-N-(8-Methoxy-1,2,3,4-Tetrahydronaphthalen-2-yl)acetamide, (R)-1 b

The same procedure was used as for the synthesis of (*S*)-**1 a**, using amine **3 b** (100 mg, 0.56 mmol), NEt_3 (235 µL, 1.68 mmol) and acetyl chloride (59 µL, 0.84 mmol) to give (*R*)-**1 b** (111 mg, 91%). The NMR spectroscopic characterisation data was the same as for **1 a**. M.p. 107 °C (Et_2O); $[\alpha]^{20}_D$ +29.1 (*c* 0.5, CH_2Cl_2); *m/z* [EI] 219 ($[M]^+$, 100%), 145, 129, 115; *m/z* [HRMS EI] found 219.1254 $[M]^+$. $C_{13}H_{17}NO_2$ requires 219.1254.

(2S)-8-Methoxy-N-propyl-1,2,3,4-tetrahydronaphthalen-2-amine

To a solution of (*S*)-**1 a** (137 mg, 0.77 mmol) in MeCN (20 mL), K_2CO_3 (319 mg, 2.31 mmol) and 1-bromopropane (139 µL, 1.54 mmol) were added. The reaction was heated at reflux for 48 h then concentrated under vacuum and CH_2Cl_2 (20 mL) and HCl (0.1 M, 10 mL) added. The aqueous layer was washed with CH_2Cl_2 (3×20 mL) and basified with NaOH (0.1 M) to pH 12, then re-extracted with CH_2Cl_2 (3×20 mL). The combined organic phase was dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by silica column chromatography (80% petroleum ether (40–60)/20% EtOAc to 20% petroleum ether (40-60)/80% EtOAc) to afford the titled compound (106 mg, 63%). $[\alpha]^{20}_D$ −63.2 (*c* 0.5, CH_2Cl_2) [lit. $[\alpha]^{23}_D$ −70.9 (MeOH)[42]]; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 7.09 (1H, t, *J* = 8.2 Hz, 6-H), 6.72 (1H, d, *J* = 8.2 Hz, 5-H or 7-H), 6.66 (1H, d, *J* = 8.2 Hz, 5-H or 7-H), 3.81 (3H, s, OMe), 3.13–3.06 (1H, m), 2.94–2.80 (3H, m), 2.71 (2H, t, *J* = 7.5 Hz, NCH_2CH_2), 2.35–2.26 (1H, dd, *J* = 16.6 and 8.9 Hz, 1-H*H*), 2.06–1.98 (1H, m), 1.62–1.49 (3H, m, NCH_2CH_2, 3-H*H*), 0.96 (3H, t, *J* = 7.5 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 157.6, 137.9, 126.2, 124.5, 121.0, 107.0, 55.4, 53.7, 49.3, 30.7, 29.7, 28.5, 23.8, 12.1; *m/z* [ES+] 220

([MH]$^+$, 100%); *m/z* [HRMS ES+] found 220.1701 [MH]$^+$. $C_{14}H_{22}NO$ requires 220.1700.

(2R)-8-Methoxy-N-propyl-1,2,3,4-tetrahydronaphthalen-2-amine

The same procedure was used as for the synthesis of the (2*S*)-isomer, using amine **1b** (130 mg, 0.73 mmol) in MeCN (20 mL), K_2CO_3 (302 mg, 2.19 mmol) and 1-bromopropane (131 µL, 1.46 mmol) to give the titled compound (91 mg, 56%). The NMR spectroscopic characterisation data was the same as for the (2*S*)-isomer. $[\alpha]^{20}_D$ +56.2 (*c* 0.5, CH_2Cl_2) [lit. $[\alpha]^{23}_D$ +67 (MeOH)[42]]; *m/z* [ES+] 220 ([MH]$^+$, 100%); *m/z* [HRMS ES+] found 220.1701 [M]$^+$. $C_{14}H_{22}NO$ requires 220.1701.

(2S)-N-(8-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-N-propylpropionamide

To a solution of (2*S*)-8-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (101 mg, 0.46 mmol) in CH_2Cl_2 (15 mL) under argon, NEt_3 (193 µL, 1.38 mmol) followed by propionyl chloride (64 µL, 0.69 mmol) at 0 °C were added. The reaction was increased to rt and and stirred for 4 h. The reaction mixture was washed with HCl (0.1 M; 3 × 10 mL) and NaOH (0.05 M, 3 × 10 mL). The organic phase was then dried ($MgSO_4$) and concentrated under vacuum to afford the titled compound[43] (112 mg, 89%). $[\alpha]^{20}_D$ −86.7 (*c* 0.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$; 500 MHz) (Two rotamers, ratio ~1:1) δ 7.15–7.05 (1H, m, 6-H), 6.75–7.63 (1H, m, 5-H, 7-H), 4.70–4.63 (0.5H, m, 2-H) and 4.02–4.96 (0.5H, m, 2-H), 3.81 (1.5H, s, OMe) and 3.79 (1.5H, s, OMe), 3.31–3.25 (0.5H, m), 3.18-3.08 (1.5H, m,), 2.97–2.85 (3H, m), 2.66–2.54 (1H, m), 2.41–2.34 (2H, m) 1.98–1.87 (2H, m), 1.72–1.56 (2H, m), 1.19–1.13 (3H, 2 x t, *J* = 7.5 Hz, $COCH_2CH_3$), 0.93–0.88 (3H, m, $CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$; 125 MHz) (Two rotamers, ratio ~ 1:1) δ 174.0 and 173.4, 157.4, 137.1 and 136.6, 126.7 and 126.3, 124.6 and 123.8, 120.9, 107.1 and 107.0, 55.3, 53.9 and 51.3, 46.1 and 43.9, 30.0, 28.5 and 28.2, 27.6 and 27.1, 27.03 and 27.01, 24.8 and 23.1, 11.8 and 11.6, 9.91 and 9.84; *m/z* [ES+] 276 ([MH]$^+$, 100%); *m/z* [HRMS ES+] found 276.1965 [MH]$^+$. $C_{17}H_{26}NO_2$ requires 276.1964.

(2R)-N-(8-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-N-propylpropionamide

The same procedure was used as for the synthesis of the (2*S*)-isomer, using (2*R*)-8-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (80 mg, 0.36 mmol) in CH_2Cl_2 (12 mL), NEt_3 (151 µL, 1.08 mmol) and propionyl chloride (47 µL, 0.54 mmol). The crude mixture was purified by column chromatography (90% petroleum ether (40-60)/10% EtOAc to 70% petroleum ether (40–60)/30% EtOAc) to afford the titled compound[43] (73 mg, 75%). The NMR spectroscopic characterisation data was the same as for the (2*S*)-isomer. $[\alpha]^{20}_D$ +62.4 (*c* 0.5, CH_2Cl_2)]; *m/z* [ES+] 276.5 ([MH]$^+$, 100%); *m/z* [HRMS ES+] found 276.1962 [M]$^+$. $C_{17}H_{26}NO_2$ requires 276.1964.

(2S)-8-Methoxy-N,N-dipropyl-1,2,3,4-tetrahydronaphthalen-2-amine

To a solution of (2*S*)-*N*-(8-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylpropionamide (98 mg, 0.36 mmol) in dry CH_2Cl_2 (12 mL) under argon at 0 °C, was added lithium aluminium hydride (450 µL, 1.80 mmol; 4 M in Et_2O) dropwise. The reaction was warmed to rt and left to stir for 3 h. The reaction was then quenched at 0 °C with water (10 mL). The product was extracted with CH_2Cl_2 (3 × 10 mL) and the organic phases were dried ($MgSO_4$) and concentrated under vacuum to afford the titled compound (91 mg, 97%). $[\alpha]^{20}_D$ −68.4 (*c* 0.5, CH_2Cl_2) [lit. $[\alpha]^{22}_D$ −76.1 for the HCl salt (c 1.03, MeOH)[44]]; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 7.08 (1H, t, *J* = 8.4 Hz, 6-H), 6.71 (1H, d, *J* = 8.4 Hz, 5-H or 7-H), 6.66 (1H, d, *J* = 8.4 Hz, 5-H or 7-H), 3.82 (3H, s, OMe), 2.98–2.92 (2H, m), 2.90–2.80 (2H, m), 2.50 (4H, t, *J* = 7.9 Hz, 2 × NCH_2), 2.45-2.40 (1H, m), 2.01–1.96 (1H, m), 1.65–1.57 (1H, m), 1.52–1.44 (4H, m, 2 × CH_2CH_3), 0.90 (6H, t, *J* = 6.6 Hz, 2 × CH_2CH_3); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 157.7, 138.1, 126.0, 125.5, 120.9, 106.9, 57.0, 55.3, 52.8, 30.3, 26.0, 25.4, 22.4, 12.1; *m/z* [ES+] 262 ([MH]$^+$, 100%); *m/z* [HRMS ES+] found 262.2169 [MH]$^+$. $C_{17}H_{28}NO$ requires 262.2165.

(2R)-8-Methoxy-N,N-dipropyl-1,2,3,4-tetrahydronaphthalen-2-amine

The same procedure was used as for the synthesis of the (2*S*)-isomer, using (2*R*)-*N*-(8-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylpropionamide (65 mg, 0.24 mmol) in dry CH_2Cl_2 (8 mL) and lithium aluminium hydride (300 µL, 1.20 mmol; 4 M in Et_2O) to give the titled compound (62 mg, 100%). The NMR spectroscopic characterisation data was the same as for the (2*S*)-isomer. $[\alpha]^{20}_D$ +61.2 (*c* 0.5, CH_2Cl_2) [lit. $[\alpha]^{22}_D$ +77.1 for the HCl salt (c 1.04, MeOH)[44]]; *m/z* [ES+] 262 ([MH]$^+$, 100%); *m/z* [HRMS ES+] found 262.2167 [MH]$^+$. $C_{17}H_{28}NO$ requires 262.2165.

(2S)-7-(Dipropylamino)-5,6,7,8-tetrahydronaphthalen-1-ol 2a

To a solution of (2*S*)-8-methoxy-*N*,*N*-dipropyl-1,2,3,4-tetrahydronaphthalen-2-amine (76 mg, 0.29 mmol) in dry CH_2Cl_2 (4 mL) and under argon at 0 °C, was added boron tribromide solution (580 µL, 0.58 mmol; 1 M BBr_3 in CH_2Cl_2). The reaction was warmed to rt and stirred for 4 h, then quenched at 0 °C with the slow addition of HCl (0.1 M; 4 mL). The aqueous layer was washed with CH_2Cl_2 (3 × 10 mL) and basified with NaOH (0.1 M) to pH 12, then re-extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum to afford **2a** as a colorless oil (69 mg, 96%). $[\alpha]^{20}_D$ −67.6 (*c* 0.5, CH_2Cl_2) [lit. $[\alpha]^{22}_D$ −66.5 for the HBr salt (c 1.01, MeOH)[44]; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 6.98 (1H, t, *J* = 8.1 Hz, 3-H), 6.67 (1H, d, *J* = 8.1 Hz, 2-H or 4-H), 6.59 (1H, d, *J* = 8.1 Hz, 2-H or 4-H), 4.78 (1H, br s, OH), 3.05–2.74 (4H, m), 2.53 (4H, t, *J* = 7.4 Hz, 2 × NCH_2), 2.48–2.41 (1H, m), 2.05–2.00 (1H, m), 1.67–1.59 (1H, m), 1.57-1.44 (4H, m, 2 × CH_2CH_3), 0.90 (6H, t, *J* = 7.4 Hz, 2 × CH_2CH_3); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 154.1, 138.4, 126.3, 123.4, 120.9, 112.1, 57.1, 52.8, 30.4, 25.8, 25.5 22.1, 12.1; *m/z* [ES+] 248 ([MH]$^+$,

100%); *m/z* [HRMS ES+] found 248.2012 $[MH]^+$. $C_{16}H_{26}NO$ requires 248.2014.

(2S)-7-(Dipropylamino)-5,6,7,8-tetrahydronaphthalen-1-ol 2 b

The same procedure was used as for the synthesis of (2*S*)-**2 a**, but using (2*R*)-8-methoxy-*N*,*N*-dipropyl-1,2,3,4-tetrahydronaphthalen-2-amine (58 mg, 0.22 mmol) in dry CH_2Cl_2 (3 mL) and boron tribromide solution (440 µL, 0.44 mmol; 1 M BBr_3 in CH_2Cl_2), to give **2 b** as a colorless oil (54 mg, 91%). The NMR spectroscopic characterisation data was the same as for the (2*S*)-isomer. $[\alpha]^{20}_D$ +52.8 (*c* 0.5, CH_2Cl_2) [lit. $[\alpha]^{22}_D$ +67.5 for the HBr salt (c 1.03, MeOH)[44]]; *m/z* [ES+] 248 ($[MH]^+$, 100%); *m/z* [HRMS ES+] found 248.2019 $[MH]^+$. $C_{16}H_{26}NO$ requires 248.2014.

Derivatisation of (2S)-3 a with (2S)-α-Methoxy-α-trifluoromethylphenylacetic Acid ((2S)-MTPA)

To a solution of (2*S*)-**3 a** (10 mg, 0.056 mmol) in dry CH_2Cl_2 (1 mL) under argon was added DCC (12.7 mg, 0.062 mmol) and DMAP (1.3 mg, 0.011 mmol), followed by (2*S*)-MTPA (9.8 µL, 0.062 mmol) at 0 °C. The reaction was stirred at rt for 6 h, concentrated under vacuum and purified by silica column chromatography (100% petroleum ether (40-60) to 30% petroleum ether (40-60)/70% EtOAc) to afford the (2*S*)-Mosher's ester of (2*S*)-**3 a** (18 mg, 82%). ^{1}H NMR ($CDCl_3$; 300 MHz) δ 7.57–7.52 (2H, m, Ph), 7.42–7.39 (3H, m, Ph), 7.11 (1H, t, *J* = 8.4 Hz, 6-H), 6.81–6.66 (3H, m, NH, 5-H and 7-H), 4.36–4.27 (1H, br m, C*H*NH), 3.82 (3H, s), 3.43 (3H, s), 3.16 (1H, dd, *J* = 17.6 and 6.5 Hz, 1-*H*H), 2.94–2.72 (2H, m), 2.47 (1H, dd, *J* = 17.6 and 9.0 Hz, 1-H*H*), 2.07–2.00 (1H, m), 1.75–1.64 (1H, m); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 165.9, 157.6, 136.9, 133.0, 129.6, 128.7, 127.7, 126.7, 122.9, 121.0, 107.2, 55.4, 55.1, 45.6, 29.7, 28.3, 27.6; *m/z* [CI] 394 ($[MH]^+$, 100%); *m/z* [HRMS CI] found 394.1625 $[MH]^+$. $C_{21}H_{23}F_3NO_3$ requires 394.1625.

Derivatisation of (2S)-3 a with (2R)-MTPA

To a solution of (2*S*)-**3 a** (10 mg, 0.056 mmol) in dry CH_2Cl_2 (1 mL) under argon was added DCC (12.7 mg, 0.062 mmol) and DMAP (1.3 mg, 0.011 mmol), followed by (2*R*)-MTPA (9.8 µL, 0.062 mmol) at 0 °C. The reaction was stirred at rt for 6 h, concentrated under vacuum and purified by silica column chromatography (100% petroleum ether (40-60) to 30% petroleum ether (40-60)/70% EtOAc) to afford the (2*R*)-Mosher's ester of (2*S*)-**3 a** (17 mg, 79%). ^{1}H NMR ($CDCl_3$; 300 MHz) δ 7.56–7.52 (2H, m, Ph), 7.43–7.40 (3H, m, Ph), 7.12 (1H, t, *J* = 8.4 Hz, 6-H), 6.90–6.88 (1H, br d, *J* = 8.4 Hz, NH), 6.74 (1H, d, *J* = 8.4 Hz, 5-H or 7-H), 6.67 (1H, d, *J* = 8.4 Hz, 5-H or 7-H), 4.35–4.26 (1H, br m, C*H*NH), 3.81 (3H, s), 3.37 (3H, s), 3.10 (1H, dd, *J* = 17.6 and 6.5 Hz, 1-*H*H), 2.92–2.80 (2H, m), 2.47 (1H, dd, *J* = 17.6 and 9.0 Hz, 1-H*H*), 2.14–2.06 (1H, m), 1.84–1.72 (1H, m); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 165.9, 157.5, 137.0, 132.6, 129.6, 128.7, 127.9, 126.7, 123.0, 121.1, 107.2, 55.4, 55.1, 45.7, 29.6, 28.5, 27.6; *m/z* [CI] 394 ($[MH]^+$, 100%); *m/z* [HRMS CI] found 394.1625 $[MH]^+$. $C_{21}H_{23}F_3NO_3$ requires 394.1625.

Derivatisation of (2R)-3 b with (2R)-MTPA-Cl

To a solution of (2*S*)-**3 b** (12 mg, 0.067 mmol) in dry CH_2Cl_2 (2 mL) under argon was added NEt_3 (28 µL, 0.21 mmol), followed by (2*R*)-MTPA–Cl (18 µL, 0.11 mmol) at 0 °C. The reaction was stirred at rt for 2 h, quenched with HCl (1 mL; 0.1 M), extracted with CH_2Cl_2 (3 × 2 mL), washed with NaOH (2 mL; 0.1 M) and dried ($MgSO_4$). It was concentrated under vacuum to afford the (2*S*)-Mosher's ester of (2*R*)-**3 b** (20 mg, 74%). ^{1}H NMR ($CDCl_3$; 300 MHz) δ 7.56–7.52 (2H, m, Ph), 7.43–7.40 (3H, m, Ph), 7.12 (1H, t, *J* = 8.4 Hz, 6-H), 6.90–6.88 (1H, br d, *J* = 8.4 Hz, NH), 6.74 (1H, d, *J* = 8.4 Hz, 5-H or 7-H), 6.67 (1H, d, *J* = 8.4 Hz, 5-H or 7-H), 4.35–4.26 (1H, br m, C*H*NH), 3.81 (3H, s), 3.37 (3H, s), 3.10 (1H, dd, *J* = 17.6 and 6.5 Hz, 1-*H*H), 2.92–2.80 (2H, m), 2.47 (1H, dd, *J* = 17.6 and 9.0 Hz, 1-H*H*), 2.14–2.06 (1H, m), 1.84–1.72 (1H, m); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 165.9, 157.5, 137.0, 132.6, 129.6, 128.7, 127.9, 126.7, 123.0, 121.1, 107.2, 55.4, 55.0, 45.7, 29.6, 28.5, 27.6; *m/z* [ES+] 394 ($[MH]^+$, 100%); *m/z* [HRMS ES+] found 394.1635 $[MH]^+$. $C_{21}H_{23}F_3NO_3$ requires 394.1625.

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RESEARCH ARTICLE

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